2. SYNOPSIS

Name of Sponsor: Dicerna Pharmaceuticals, Inc., a Novo Nordisk company, Lexington. MA USA

Name of Finished Product: DCR-A1AT, also known as belcesiran and NN6021

Name of Active Ingredient: DCR-S1459, also known as belcesiran sodium

Title of Study: A Phase 2, Randomized, Double-blind, Placebo-controlled Study Investigating Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Two Dose Levels of Belcesiran in Patients with Alpha-1 Antitrypsin -Associated Liver Disease

Investigator(s) and Study Center(s): This study was conducted at 23 centers in Australia, Austria, Belgium, Canada, France, Germany, Ireland, Netherlands, New Zealand, Portugal, Spain, Sweden, the United Kingdom, and the United States.

Publication(s): None as of the date of this report

Study Period: 08 December 2023 to 16 April 2024

Development Phase: 2

Previous Reports for This Study: None

Objectives:

Primary (Cohorts 1 and 2)

1. To evaluate the safety and tolerability of multiple doses of belcesiran in patients with AATLD
2. To characterize the PD of belcesiran in patients with AATLD

Primary (Cohort 3)

1. To characterize the PD of belcesiran in patients with AATLD

Secondary

1. To characterize the PK of belcesiran in the plasma of patients with AATLD
2. To assess the effect of belcesiran on liver histology in patients with AATLD

Methodology:

Number of Participants Planned: 46

Number of Participants Analyzed: 16

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

- 18 to 75 years, inclusive, at the time of consent.
- Documented diagnosis of PiZZ-type alpha-1 antitrypsin deficiency, confirmed by genotyping. Historical genotyping data was used, if available.
- AATD-associated liver disease documented by liver biopsy at Screening.
- Consent to undergo paired liver biopsies.
- Lung, renal, and liver function within acceptable limits

- Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Exclusion Criteria:

- History of chronic liver disease other than non-alcoholic fatty liver disease from any cause other than PiZZ-type alpha-1 antitrypsin deficiency.
- Child-Pugh Score B or C.
- History of one single severe exacerbation of underlying lung disease in the year prior to randomization.
- History of clinically significant respiratory infections (including pneumonia and lower respiratory tract infections), as determined by the Investigator, in the 3 months prior to screening
- Use of an RNAi drug at any time.

Investigational Product, Dose, and Mode of Administration: Belcesiran is supplied as a solution of the drug substance (belcesiran sodium) in water for injection.

Arm Name	Active		Placebo
Intervention name	belcesiran		0.9% saline for injection
Intervention type	Drug		Drug
Dose formulation	solution for injection		solution for injection
	Sodium salt	Free acid	
Drug product concentration	185 mg/mL	175 mg/mL	n/a
Route of administration	SC injection (thigh or abdomen)		SC injection (thigh or abdomen)
IMP or NIMP	IMP		n/a
Sourcing	Provided centrally by the Sponsor or designee		Provided locally by the trial site
Packaging and labeling	Belcesiran will be provided in vials. Each vial will be labeled as required per country.		n/a

Abbreviations: IMP: investigational medicinal product; n/a: not applicable; NIMP: non-investigational medicinal product; SC: subcutaneous.

Duration of Treatment:

- Participants in Cohort 1 were randomized to either belcesiran [redacted] mg or placebo. Participants had the option to continue treatment for an additional 72 weeks so that the total treatment duration would have been 96 weeks.
- Participants in Cohort 2 were randomized to either belcesiran [redacted] mg or placebo. Participants had the option to continue treatment for an additional 48 weeks so that the total treatment duration would have been 96 weeks.

- Participants in Cohort 3 would have been randomized to belcesiran [redacted] mg, the equivalent amount of placebo for belcesiran [redacted] mg, belcesiran [redacted] mg or the equivalent amount of placebo for belcesiran [redacted] mg. Participants would have been blinded within each dose level. Participants continued treatment until 96 weeks of treatment have been completed.

Participants in Cohorts 1 (and 3) received (or would have received) monthly dosing for the first 24 weeks then shifted to quarterly dosing thereafter until week 96. Participants in Cohort 2 received monthly dosing for the first 48 weeks and then shifted to quarterly dosing thereafter until week 96. Participants continued the IMP throughout the study, unless the participant or investigator decided to discontinue IMP, or the participant withdrew from the trial or a discontinuation criterion was met.

All Participants in Cohorts 1 to 3 had (or would have had) the option to undergo a liver biopsy at EOT/week 96. Biopsy findings were expected to be correlated with changes in non-invasive markers of liver disease and liver stiffness.

After the EOT visit, all participants were planned to be followed up for 48 weeks. Cohorts 1 and 2 were planned to be followed for an additional 48 weeks (total of 96 weeks after EOT) to inform about the duration of potential treatment effects. If a participant in Cohorts 1 or 2 did not wish to extend the treatment period to 96 weeks, follow-up would have stopped after the 48-week follow-up period.

Criteria for Evaluation

Pharmacokinetics: No PK analysis was performed for the present report.

Safety: The incidence and nature of TEAEs, and the change from Baseline in PFTs, 12 lead ECGs, physical examination findings, vital signs, and clinical laboratory tests

Statistical Methods:

Summary statistics (n, mean, standard deviation, median, minimum and maximum values for continuous variables, and number and percentage of participants in each category for categorical variables) are provided by treatment group and cohort for all variables.

Baseline value was defined as the last non-missing assessment prior to the first dose of study drug, except for serum AAT where baseline was defined as the mean from all predose AAT measurements.

Source data for the summary tables are presented as by-subject data listings.

All statistical tests are 1-sided with a type I error rate of 5%, unless otherwise specified.

Summary of Results

Participant Disposition:

A total of 41 participants were screened for participation in the study; of these, 25 (61%) were considered screen failures. The remaining 16 participants were randomized to receive either active study drug or placebo. Cohort 1 and cohort 2 enrolled 8 participants each, with 11 and 5 participants being assigned to active drug or placebo, respectively. Of the total 16 randomized and treated participants, 11 (68.8%) completed the treatment period. Of the 5 who discontinued the treatment period, 4 discontinued due to the study’s termination, and 1 withdrew (“withdrawal by subject”). The 11 participants who completed the treatment period did not complete the follow up period.

The Enrolled Population (N=41) is defined as all participants who signed the informed consent form. The Safety Population (N=16) is defined as all participants randomly assigned to study intervention who have received at least 1 dose of the study drug (DCR-A1AT or placebo). The PD (Pharmacodynamic) Population (N=16) is defined as all participants randomly assigned to study intervention who received at least 1 dose of DCR-A1AT (or placebo) and at least 1 postdose PD assessment. The Evaluable Population (N=13) is defined as all participants randomly assigned to study intervention and who received at least 50% of planned doses of belcesiran/placebo. No hypothesis tests was performed due to the early termination of the study. All data including demographic, PD and safety parameters are summarized using descriptive statistics. The PK and evaluable population will not be considered for the analysis due to the early termination of the study.

Baseline Demographics:

Characteristic Statistic Statistic/Category	Pooled Placebo	Belcesiran		Active Total	Total
		Cohort 1 (7 doses)	Cohort 2 (13 doses)		
	N=5	N=5	N=6	N=11	N=16
Age (years)[a]					
Mean	40.2	57.2	52.5	54.6	50.1
Standard Deviation	17.31	10.18	11.86	10.86	14.36
Median	49.0	56.0	55.0	56.0	54.0
Min, Max	19.0, 55.0	45.0, 68.0	32.0, 66.0	32.0, 68.0	19.0, 68.0
Q1, Q3	24.0, 54.0	50.0, 67.0	47.0, 60.0	47.0, 66.0	46.0, 58.0
Sex, n (%)					
Male	4 (80.0)	2 (40.0)	4 (66.7)	6 (54.5)	10 (62.5)
Female	1 (20.0)	3 (60.0)	2 (33.3)	5 (45.5)	6 (37.5)
Race, n (%)					
White	5 (100.0)	5 (100.0)	6 (100.0)	11 (100.0)	16 (100.0)
Ethnicity, n (%)					
Not Hispanic or Latino	5 (100.0)	5 (100.0)	6 (100.0)	11 (100.0)	16 (100.0)

[a] Age in years is calculated based on the number of years between the informed consent date and the birth date.

Safety Results:

- Belcesiran was generally safe and well tolerated in participants with alpha-1 antitrypsin-associated liver disease.
- TEAEs occurring in 3 or more participants included COVID-19, upper respiratory tract infection, and cough.
- Most TEAEs were classified as “Not Related” to the study medication.
- Eight out of the 150 total reported TEAEs were related to the administration site, 1 met the protocol-defined definition of ISR and was classified as a Grade 1 ISR.
- Four participants (14 events) in the placebo group and for 9 participants (26 events) who received belcesiran. Study drug-related TEAEs reported by the placebo group were mild to moderate in

severity. All but 1 study drug-related TEAE reported by the participants who received belcesiran group were mild to moderate. The 1 participant with a severe study drug-related TEAE was in Cohort 1.

- One instance of complement factor C4 increase was reported in a participant in Cohort 1. This was considered a to be study drug-related TEAE and was graded as mild in severity.
- There were no treatment- or dose-related trends in coagulation parameters, liver (ALT, ALP, and AST), or kidney function.
- No treatment- or dose-related trends in PFTs, including percent predicted FEV1, percent predicted FVC, FEV1/FVC ratio, and percent predicted DLCO, were observed either during the treatment period or the follow-up period. The lack of clinically significant changes in key spirometry parameters and lack of TEAEs related to pulmonary function is indicative of the acceptable safety profile of belcesiran.
- Four participants receiving belcesiran reported a total of 12 SAEs; of these SAEs, 8 were judged by the investigator to be not related to the study drug. In all but 2 SAEs, the study drug did not need to be interrupted. All participants recovered and all SAEs resolved.

Conclusions:

- Doses of belcesiran were generally safe and well-tolerated when administered as multiple doses in participants with PiZZ AATLD (liver fibrosis stage 1-4, METAVIR scoring system). The majority of TEAEs were mild in severity. No treatment- or dose-related trends in the frequency, severity, or relatedness of TEAEs were observed. Injection site reactions were reported in 1 participant receiving belcesiran. There were no treatment- or dose-related clinically significant trends in the hematology, biochemistry, vital signs, physical examinations, ECGs, or urine analyses during the study.
- Repeated administration of belcesiran resulted in a decrease in serum AAT protein concentration in individuals with PiZZ AATLD. The reduction in serum AAT levels at week 24 compared to baseline was more pronounced among participants who were administered belcesiran than those given placebo.
- Upon employing a linear regression model, it was observed that at week 24, participants in the belcesiran group experienced a reduction of 68.96% in serum AAT levels, while there was a 13.46% reduction in the pooled placebo arm. Furthermore, the reduction in the belcesiran group was significantly greater, at 55.50% percent reduction, with a 95% confidence interval of (-76.77%, -34.23%), compared to the placebo group.
- The time to maximal AAT reduction from baseline among the pooled active belcesiran group was approximately at 8 weeks. Some participants did not complete the study due to study early termination.
- Belcesiran produced reduction in serum AAT protein concentrations when administered as repeated doses in participants with PiZZ AATLD; a potential long-lasting effect is expected with continued dosing. The results of this study support the further clinical development of belcesiran for the treatment of AATLD; however, the program was terminated for business reasons.